Role of MiRNA-204 in Glomerulonephritides

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A variety of glomerulonephritides are involved in immune complex (IC) buildup within podocytes, though little is known about how podocytes interact with ICs. The purpose of this study is to determine miR-204's role in lysosomal function when exposed to ICs. We hypothesize that upregulation of miR-204 after an immune challenge will lead to decreased lysosomal function, resulting in podocyte protection. MiR-204 expression was examined in cultured mouse podocytes using miRNA-seq. IF was used to examine lysosomal morphology in cells after IC treatment and using a miR-204 mimic or inhibitor. Expression of LAMP1, a lysosomal marker, and cathepsin D, a lysosomal enzyme were assessed using western blot analysis. Lysosomal activity was examined by using fluorescent recovery after photobleaching (FRAP). MiRNA-seq showed that IC treatment increased miR-204 expression. Microscopy revealed that cells treated with ICs had larger lysosomes clustering around the nucleus. FRAP showed that IC exposure decreased cathepsin B activity. Upregulation of miR-204 led to decreased LAMP1 and cathepsin D expression. Downregulation of miR-204 induced perinuclear lysosomal clustering, whereas upregulation induced cytoplasmic lysosomal dispersion. Our data suggest that an immune challenge induces lysosomal activation, and upregulation of miR-204 decreases lysosomal activity. We hypothesize that chronic lysosomal activation in podocytes is deleterious and that miR-204 exerts a protective effect by diminishing chronic lysosomal activation. Our next steps involve utilizing miR-204 KO mice. IC disease in these mice will be induced by utilizing the Nephrotoxic Serum Nephritis model, injecting nephrotoxic serum into a vein in the tail, and measuring blood and urine to assess the renal response.